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Visual Case Discussion

Hydroxychloroquine retinal toxicity: The bull's eye in the human eye

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1. Visual case discussion

A 52-year-old lady with history of systemic lupus erythematosus (SLE) since her late 20 s was on maintenance hydroxychloroquine (HCQ) therapy of 200 mg daily for more than 20 years. She did not suffer from any vasculitis, and was never on any steroid treatment all along. She complained of gradual insidious onset of bilateral blurring of vision. There was no eye trauma, and her SLE was well controlled with HCQ all along.

Best corrected visual acuity was Snellen decimal 0.4 over both eyes, despite absence of cataract. Her body weights were 62.5–70.1 kg (mean 67.7 kg) during the 20 years of HCQ therapy. Fundus examinations found abnormal pigmentation over the macula, with hyperpigmentation at center, surrounded by a ring of hypo-pigmentation in "bull's eye" target configuration. (Fig. 1) Ophthalmologists were consulted, further imaging with fundus autofluorescence scan (Fig. 2) confirmed Bull's eye maculopathy by HCQ toxicity from current clinical context.

Under the pandemic of coronavirus disease 2019 (COVID-19), novel treatment with HCQ was attempted to fight against the virus. Despite controversial risks and benefits of HCQ treatment on COVID-19, HCQ is well known to doctors for their side effects in long term usage, especially the ocular toxicity.

Originally an anti-malarial drug, HCQ is widely used in rheumatologists' hands for long on treating SLE, rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and Sjogren's syndrome. Its main immuno-modulatory effect is evidenced clinically on cutaneous and musculoskeletal manifestations, and is effective to prevent flare up. Thus, patients are often put on HCQ for years as maintenance therapy.

Despite the difference in retinal involvement by HCQ toxicity of Asian from Caucasian,¹ standard screening guidelines do exist from ophthalmology authorities.² HCQ can deposit over the cornea and posterior lens capsule to hinder vision, whereas deposition over the ciliary body would cause difficulties in accommodation. Concerning the retina, HCQ binds to melanin in the retinal pigment epithelium (RPE), inhibiting its function to cause irreversible photoreceptor loss, thus visual field defect over affected area. This RPE dysfunction causing atrophy usually happens over the perifoveal ring area sparing the central fovea, thus resulting in Bull's eye configuration on imaging (Fig. 2) and corresponding Bull's eye ring scotoma on visual field test. The accepted safety daily dosage of HCQ is 5 mg/kg, yet risk of HCQ toxicity increases with > 20 years' consumption despite usage under the safety dose (as in our case).³ Early detection of HCQ retinal toxicity is essential, as maculopathy could progress after cessation of HCQ given its long half-life of 1 month, which translates to 6 months of washout period for full elimination from the body.

Although Bull's eye macula is very characteristics in configuration on clinical examination, it is not specific to HCQ toxicity alone. Both congenital and systemic diseases could manifest as Bull's eye patterned macula, such as fleck retina syndrome in Stargardt's disease, Bardet-Biedl syndrome, Leber's congenital amaurosis, cone dystrophy, neuronal ceroid lipofuscinoses etc. Therefore, clinical history and bilateral eye examinations are essential for arriving the definite diagnosis.

In conclusion, HCQ usage is increasing under the COVID-19 pandemic, but physicians should be aware of the clinical signs of HCQ retinal toxicity, such as Bull's eye maculopathy.

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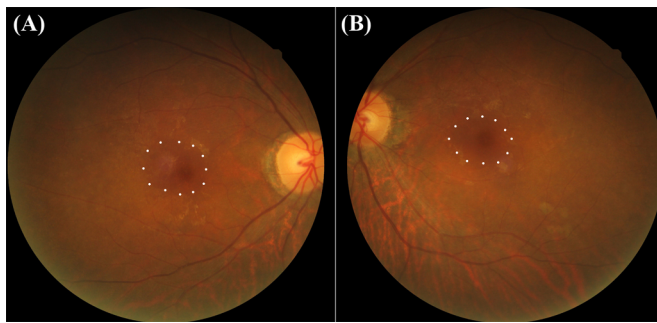


Fig. 1. . Colored fundus photos of right (A) and left (B) eye of the patient with >20 years of hydroxychloroquine (HCQ) treatment of mean dosage 2.95 mg/kg/day. White dots circled area outlined the Bull's eye macular configuration in HCQ retinal toxicity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

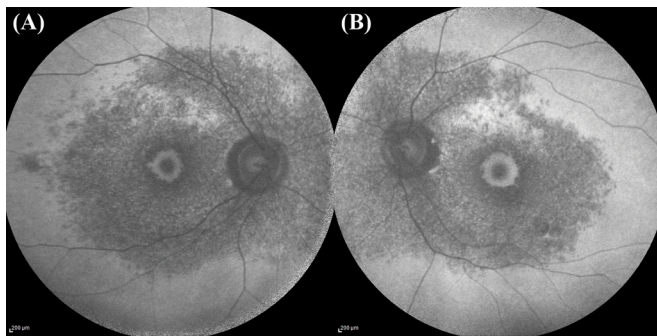


Fig. 2. . Fundus autofluorescence (FAF) photos of right (A) and left (B) eye of the patient few months after Fig. 1 was taken. Progression of Bull's eye maculopathy was evidenced by the concentric rings over the fovea. Normal retinal pigment epithelium (RPE) is autofluorescence, appearing as white color on FAF, as in the peripheral part of (A) & (B). Hypo-autofluorescence appears as black color on FAF, and the areas signified the atrophy of the melanin containing RPE (other than the optic disk and the retinal vasculature).

2. Question 1

Which of the following disease is treated by hydroxychloroquine?

- A) Bardet-Biedl syndrome
- B) Cone dystrophy
- C) Leber's congenital amaurosis
- D) Stargardt's disease
- E) Systemic lupus erythematosus

Correct answer: (E) Systemic lupus erythematosus

2.1. Discussion & rationale

Hydroxychloroquine is used in treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and Sjogren's syndrome.

Bardet-Biedl syndrome, cone dystrophy, Leber's congenital amaurosis and Stargardt's disease are disease entities with Bull's eye configuration over the macula, simulating Bull's eye maculopathy from hydroxychloroquine toxicity.

3. Question 2

Bull's eye maculopathy can be detected primarily in which of the following disease?

- a) Central retinal artery occlusion
- b) Commotio retinae
- c) Cone dystrophy
- d) Macula hole
- e) Sjogren's syndrome

Correct answer: (C) Cone dystrophy.

3.1. Discussion & rationale

Bull's eye maculopathy could be detected in Stargardt's disease, Bardet-Biedl syndrome, Leber's congenital amaurosis, and cone dystrophy.

Central retinal artery occlusion, commotion retinae and macular hole could cause cherry-red spot over the central macula, but not Bull's eye maculopathy.

The disease of Sjogren's syndrome itself does not affect the macula, unless patients suffered from hydroxychloroquine toxicity by treatment.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.visj.2020.100818](https://doi.org/10.1016/j.visj.2020.100818).

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